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(71) Applicant (*for all designated States except US*): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): ANDERSON, Neil, Robert [US/US]; 906 Northwestern Avenue, West Lafayette, IN 47906 (US). WIRTH, David, Dale [US/US]; 5851 Farm Ridge Road, West Lafayette, IN 47906 (US).

(74) Agents: MCNEIL, Scott, Alexander et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

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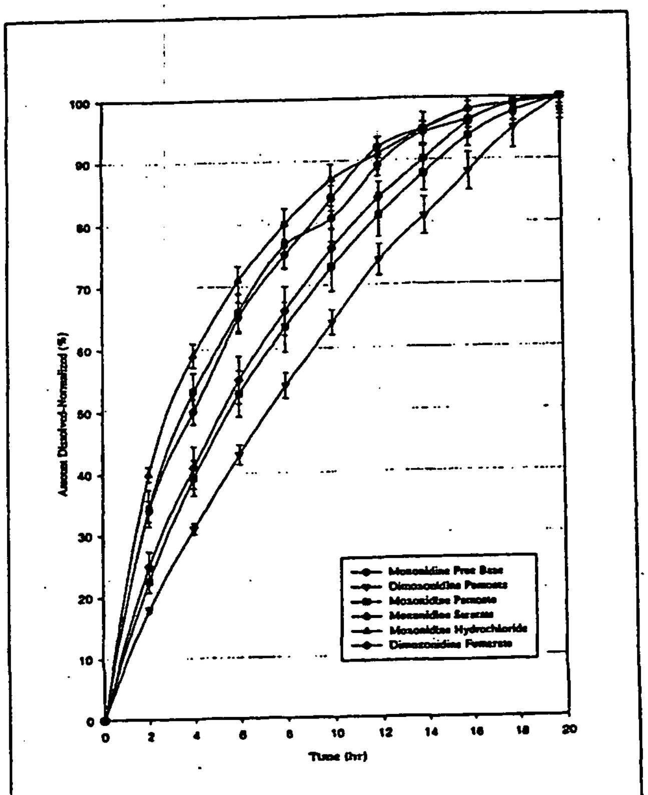
(54) Title: MOXONIDINE SALTS

(57) Abstract

This invention comprises a low solubility salt of moxonidine and pharmaceutical formulations, containing a low solubility moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low solubility moxonidine pharmaceutical formulation.



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MOXONIDINE SALTS

Related Applications

This application claims the benefit of U.S. Provisional Application No. 60/117,981, filed January 29, 1999.

Field Of The Invention

The present invention is in the fields of pharmacology and pharmaceutical chemistry and provides formulations and therapeutic methods for using salts of moxonidine which is 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methyl-pyrimidine.

Background of the Invention

Previously, predominantly alpha$_2$-adrenoceptor-agonists, such as clonidine, used as antihypertensive agents have showed a high rate of side effects, such as sedation, dry mouth and other non-specific effects. These side effects are explained by a stimulation of pre- and postsynaptic alpha$_2$-adrenoceptors within the central nervous system. Further investigations have showed that centrally acting drugs like clonidine develop their antihypertensive action through binding at imidazoline-receptors, whereas the side-effects are induced by the action at the alpha$_2$-receptors.

Moxonidine, which is also a centrally acting agent, has been shown to be effective in treating hypertension without causing the same degree of side effects associated with earlier centrally acting antihypentensive agents such as clonidine.

For moxonidine, the typical side effect is dry mouth which occurs in 2 - 15% of patients but usually improves with ongoing treatment. Other side effects like tiredness, headache and dizziness have appeared in just a few patients.

The differences between moxonidine and clonidine in clinical tolerability have been explained by the greater selectivity of moxonidine for imidazoline-receptors rather than alpha$_2$-receptors. Specifically, moxonidine is an I_1-imidazoline ligand demonstrating substantial selectivity for I_1 receptors in the centrolateral medulla over α_2 adrenergic receptors. In saturation binding experiments in bovine rostral ventrolateral medulla (bovine RVLM), moxonidine has demonstrated a selectivity for I_1 receptors that is significantly higher than that determined for clonidine (See Ernsberger et al., J. Pharmacol. Exp. Ther., 264, 172-182 (1993)).

Moxonidine is currently commercially available, at least in Germany and Austria, in immediate release formulations as an antihypertensive agent. Having been approved in Germany since 1991, there is fairly extensive clinical experience with the immediate release formulation of moxonidine. It has been found that moxonidine is almost completely absorbed from the gastrointestinal tract (absorption > 90%), that bioavailability is 88%, and that the drug does not accumulate with repeated administration. Also, plasma half life ($t_{1/2}$) has been found to be between 2 and 3 hours with a maximum plasma concentration (C_{max}) after intake of 0.2 mg of moxonidine of 1 - 3 ng/ml. While the maximum plasma level occurs in 30 - 180 minutes, the duration of the antihypertensive effect of up to 24 hours, may be due to a slower clearance of moxonidine from its central sites of action (deep compartment). Moxonidine has low plasma protein binding of 7% and is over 60% eliminated unchanged by the renal route. In patients with impaired renal function, peak plasma concentration (C_{max}), plasma half life and area under plasma concentration curve from 0 -

24 hours (AUC_{0-24}) are increased, but no accumulation occurs.

After acute administration moxonidine lowered plasma levels of norepinephrine and epinephrine, and plasma renin activity was decreased. Moxonidine has no influence on the circadian rhythm of blood pressure. No rebound phenomenon was seen after cessation of treatment.

In clinical studies 0.2 - 0.4 mg moxonidine has been found to be an effective daily dose range, with reductions in blood pressure between 10 and 20%. The antihypertensive efficacy of moxonidine was confirmed in open studies of up to 2 years duration as well as in comparative studies of up to 6 months duration.

Moxonidine has also been found to induce regression of myocardial hypertrophy, which often proceeds heart failure. In a small study, the antihypertensive effect and regression of left ventricular hypertrophy were evaluated in twenty hypertensive patients. After 6 months therapy with moxonidine, blood pressure was decreased and left ventricular septal thickness was significantly reduced from 22.5 mm to 19.1 mm (mean).

Further, moxonidine reduces systemic vascular resistance while increasing cardiac output in hypertensive patients. These hemodynamic changes may have beneficial effects in patients suffering from symptomatic congestive heart failure.

In addition, it has been demonstrated in humans that moxonidine has no detrimental effects on hemodynamic parameters in patients with congestive heart failure.

However, it has been unexpectedly discovered that administration of the current commercial formulation (immediate release formulation) of moxonidine produces an unacceptable oscillating reduction in sympathetic activity in CHF patients. A large, but transient, blood pressure

reduction has been observed 1-3 hours after dosing. This condition is likely a result of the relatively high bioavailability of moxonidine which thereby reaches peak plasma levels soon (1/2 to 3 hours) after ingestion. Both the intensity and short duration of the peak effect are undesirable.

Recently, a reduction in the undesirable blood pressure transients, previously associated with immediate release moxonidine, was achieved by administering moxonidine within sustained release formulations. However, the sustained release formulations were hard to manufacture with consistency due to the difficulty of dispersing within the formulations, with sufficient homogeneity, the small dosages of moxonidine used therein. Furthermore, it was found that these sustained release compositions were expensive to manufacture.

Therefore, a need exists for a moxonidine compound or formulation that also reduces the undesirable blood pressure transients while being easier and/or less expensive to manufacture than moxonidine sustained release formulations.

<u>Summary of the Invention</u>

The present invention relates to compounds comprising low solubility salts of moxonidine.

The invention also relates to a pharmaceutical formulation, for sustained moxonidine release, which comprises an effective dose of a low solubility moxonidine salt in association with one or more carriers, diluents or excipients.

The present invention further relates to methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising administering to a mammal in need thereof an effective dose of a low solubility moxonidine salt or a pharmaceutical formulation containing said salt.

The moxonidine salts and sustained release formulations of the present invention should afford one or more of the following advantages over the known immediate release formulations and over previously disclosed or suggested moxonidine salts: 1) minimize or eliminate side effects, particularly blood pressure oscillations and 2) improve efficiency in treatment.

Previously disclosed or suggested moxonidine acid addition salts, without additional formulation to slow and control moxonidine release rates, such as those of d-tartaric acid, maleic acid, fumaric acid, succinic acid, lactic acid, citric acid, cinnamic acid, salicylic acid, adipic acid, acetic acid, propionic acid, p-aminobenzoic acid, methanesulphonic acid, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid and benzoic acid (which are cited in U.S. Patent Nos. 4,952,410 and 5,712,283 and International Application PCT/US97/09914, published on December 11, 1997 under Publication Number W097/46241) are expected, due to their relatively high solubilities, to produce unacceptable blood pressure oscillations.

It is further anticipated the sustained release formulations of the present invention will afford more constant drug levels thereby affording improved control of the condition. In healthy humans, a geometric mean for time to maximum plasma concentration (t_{max}) should be from about 2.5 hours to about 5.0 hours, preferably 2.5 - 4.0 hours, with a geometric mean plasma elimination half-life of from about 6.0 hours to about 16.0 hours, preferably 7.0 - 15.0 hours. Thus, by employing the low solubility moxonidine salts of the present invention, once-a-day or twice-a-day administration is contemplated.

Brief Description of Drawings

FIG. 1 is a plot comparing the normalized amount of moxonidine released in water, as determined in the dissolution testing of Example 4, from tablet formulations of Example 3 of moxonidine salts of the present invention, specifically dimoxonidine pamoate, moxonidine pamoate and moxonidine stearate, as compared to moxonidine free base and the previously suggested salts moxonidine fumarate and moxonidine hydrochloride.

FIG. 2 is a plot comparing the normalized amount of moxonidine released in water, as determined in the dissolution testing of Example 4, from a tablet formulations of Example 3 of moxonidine free base as compared to previously suggested moxonidine salts, specifically dimoxonidine oxalate, dimoxonidine adipate, dimoxonidine fumarate and dimoxonidine succinate.

FIG. 3 is a plot comparing the normalized amount of moxonidine released in water, as determined in the dissolution testing of Example 4, from a tablet formulations of Example 3 of moxonidine free base as compared to previously suggested moxonidine salts, specifically moxonidine benzoate, moxonidine oxalate, moxonidine hydrochloride, dimoxonidine tartrate and dimoxonidine sulfate.

Detailed Description of the Invention

The compound of the present invention comprises a low solubility salt of moxonidine or a solvate thereof, for example, solvates with water, methanol, ethanol or other organic solvents, or mixtures of solvates. In addition, a compound of the present invention may exhibit polymorphism. Thus, compounds of the present invention also encompass any such polymorphic forms.

Low solubility is defined, herein as a solubility in aqueous media, such as water, digestive fluid, plasma or lymph, which is sufficiently low such that the administration to a mammal, in pharmaceutical formulations containing therapeutically effective doses, typically will not cause significant blood pressure oscillations. For example, moxonidine in the free base form, which when administered has resulted in significant blood pressure oscillations, does not have a suitably low solubility. The solubility for moxonidine free base, as determined through the solubility testing of Example 2, is about 1.3 mg/mL in water at 23°C.

Typically, a moxonidine salt with a suitably low solubility will have a solubility of less than 1.0 mg/mL in water at 23°C. More preferably, a low solubility salt has a solubility of less than about 0.5 mg/mL in 23°C. Most preferably, a low solubility salt of the present invention, has a solubility of less than about 0.1 mg/mL. Examples of low solubility salts of moxonidine include, for example, acid addition salts of palmitic acid or stearic acid. Preferably, the low solubility salt of the present invention is an acid addition salt of moxonidine and pamoic acid. More preferably, said salt is moxonidine pamoate which has a 1:1 molar ratio of moxondine to pamoate.

The compound moxonidine, which is a free base, is 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methyl-pyrimidine, and the method for producing moxonidine, are known and described in U.S. Patent No. 4,323,570 which is incorporated herein by reference in its entirety. A preferred synthesis of the moxonidine free base is described in U.S. Patent No. 5,732,717, and International Application PCT/US97/09914, published on December 11, 1997 under Publication Number WO97/46241, which are incorporated herein by reference in their entirety.

The low solubility salts of the present invention are typically formed using conventional methods, for example the addition of an acid to the moxonidine free base. The synthesis of specific moxonidine salts of the present invention, and their solubilities, are further described, respectively, in Examples 1J - 1L and Example 2 herein.

Also, these low solubility moxonidine salts are typically isolated using conventional methods.

The low solubility salts of the present invention are suitable for treating hypertension, left ventricular hypertrophy and other conditions for which moxonidine therapy is efficacious. The term "treating" as used herein includes therapeutic and prophylaxis of the symptoms and named condition and amelioration or elimination of the condition once it has been established.

Treatment of these conditions would usually require the administration of an effective dose of low solubility moxonidine salt on a periodic basis. The term "effective dose" is meant an amount of a low solubility moxonidine salt, which will diminish or relieve one or more symptoms or conditions associated with hypertension and/or left ventricular hypertrophy, typically without causing significant blood pressure oscillations.

Typically, an effective daily dose of a moxonidine salt, of the present invention, is an amount of salt containing an equivalent weight of between about 0.01 to about 5.0 mg of moxonidine per day. As usual, the daily dose may be administered as a single dose or in divided doses, depending on the judgment of the physician in charge of the case. The preferred dose ranges for moxonidine salts may depend upon the condition to be treated, but is typically an amount of salt providing between about 0.01 to about 5.0 mg of moxonidine per day. For example, for treating hypertension, the preferred dose range is an amount

of salt providing between about 0.5 to about 1.5 of moxonidine per day.

It will be understood that the dose for a given patient is to be set by the judgment of the attending physician, and that the dose is subject to modification based on the size of the patient, the lean or fat nature of the patient, the characteristics of the particular compound chosen, the severity of the patient's symptoms and psychological factors which may affect the patient's physiological responses.

Pharmaceuticals are usually formulated into pharmaceutical dosage forms, in order to provide an easily controllable dosage of the drug, and to give the patient an elegant and easily handled product. Thus, while it is possible to administer a low solubility moxonidine salt directly, it is preferably administered in a pharmaceutical formulation comprising one or more pharmaceutically acceptable carriers, diluents or excipients and the salt. Such formulations will contain, by weight, from about 0.01 percent to about 99 percent of the moxonidine salt.

The pharmaceutical formulations of the present invention provide for the sustained release of moxonidine as compared to that obtained from moxonidine, in its free base form, or from previously disclosed or suggested moxonidine salts. Comparisons of respective moxonidine release rates are further described in Example 4 and Fig. 1 to Fig. 3, herein.

Sustained release typically includes both controlled release and prolonged release. In controlled release, relatively constant drug levels are maintained in the blood or target tissue, typically with a lower initial burst. In prolonged release, the duration of action is extended beyond that typically afforded by a conventional delivery system.

The sustained release formulations of the present invention should provide a prophylactic or therapeutic

amount of moxonidine to a patient to achieve, and then maintain, an effective dose of moxonidine with diminished undesirable effects. These formulations should achieve a more idealized temporal delivery, and possibly, spatial placement. Spatial placement relates to targeting a pharmaceutical agent to a specific organ or tissue while temporal delivery refers to controlling the rate of drug delivery.

A pharmaceutical formulation of the present invention comprises an effective dose of a low solubility moxonidine salt. In making the formulations of the present invention, a low solubility moxonidine salt will usually be mixed with at least one carrier, or diluted by at least one carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container using conventional techniques and procedures for the preparing of pharmaceutical formulations. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the formulations can be in the form of tablets, granules, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium) and soft and hard gelatin capsules.

Examples of suitable carriers, diluents and excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, liquid paraffin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragcanth, gelatin, syrup, methylcellulose, methyl- and propyl-hydroxybenzoates, vegetable oils, such as olive oil, injectable organic esters such as ethyl oleate, talc, magnesium stearate, water and mineral oil. The formulations may also include wetting agents, lubricating, emulsifying and suspending agents,

preserving agents, sweetening agents, perfuming agents, stabilizing agents or flavoring agents. The formulations of the invention can be formulated so as to enhance the sustained release characteristics of the low solubility moxonidine salt by procedures well-known in the art. Typically, the formulations of the present invention are formulated for oral administration.

Oral sustained release forms may further include diffusional systems and dissolution systems. In diffusional systems, the release rate of drug is further effected by its rate of diffusion through a water-insoluble polymer. There are generally two types of diffusional devices, reservoir devices in which a core of drug is surrounded by polymeric membrane; and matrix devices in which dissolved or dispersed drug is distributed substantially uniformly and throughout an inert polymeric matrix. In actual practice, many systems that utilize diffusion may also rely to some extent on dissolution to determine the release rate.

Common practices utilized in developing reservoir systems include microencapsulation of drug particles and press-coating of whole tablets or particles. Frequently, particles coated by microencapsulation form a system where the drug is contained in the coating film as well as in the core of the microcapsule. Drug release typically includes a combination of dissolution and diffusion with dissolution being the process that controls the release rate. Common material used as the membrane barrier coat, alone or in combination, are hardened gelatin, methyl and ethylcellulose, polyhydroxymethacrylate, polyvinylacetate, and various waxes.

In matrix systems, three major types of materials are frequently used in the preparation of the matrix systems which include insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices which have been employed

include methyl acrylate-methyl methacrylate, polyvinyl chloride and polyethylene. Hydrophilic polymers include methyl cellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxypropyl-ethylcellulose, and its derivatives and sodium carboxy-methylcellulose. Fatty compounds include various waxes such as carnauba wax, and glyceryl tristearate. Preparation of these matrix systems are by methods well known to those skilled in the art. These methods of preparation generally comprise mixing the drug with the matrix material and compressing the mixture into tablets. With wax matrixes, the drug is generally dispersed in molten wax, which is then congealed, granulated and compressed into cores. As with other sustained release systems, it is common for a portion of the drug to be available immediately as a priming dose and the remainder to be released in a sustained fashion. This is generally accomplished in the matrix system by placing a priming dose in a coat on the tablet. The coat can be applied by press coating or by conventional pan or air suspension coating. The priming coat may contain a moxonidine salt of the present invention or alternately moxonidine it the free base form.

Approaches to further reducing the dissolution rate include, for example, coating the drug with a slowly dissolving material, or incorporating the drug into a tablet with a slowly dissolving carrier. Encapsulated dissolution systems are prepared either by coating particles or granules of drug with varying thicknesses of slowly soluble polymers or by microencapsulation. The most common method of microencapsulation is coacervation, which involves addition of a hydrophilic substance to a colloidal dispersion. The hydrophilic substance, which operates as the coating material, is selected from a wide variety of natural and synthetic polymers including shellacs, waxes, starches,

cellulose acetate, phthalate or butyrate, polyvinylpyrrolidone, and polyvinyl chloride. After the coating material dissolves, the drug inside the microencapsule is immediately available for dissolution and absorption. Drug release, therefore, can be controlled by adjusting the thickness and dissolution rate of the coat. For example, the thickness can be varied from less than one μm to 200 μm by changing the amount of coating material from about 3 to about 30 percent by weight of the total weight. By employing different thicknesses, typically three of four, the active agent will be released at different, predetermined times to afford a delayed release affect. Coated particles can, of course, be directly compressed into tablets or placed into capsules.

Matrix dissolution systems are prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet. Generally there are two methods for preparing drug-polymer particles, congealing and aqueous dispersion methods. In the congealing method, the drug is mixed with a polymer or wax material and either cooled or cooled and screened or spray-congealed. In the aqueous dispersion method, the drug-polymer mixture is simply sprayed or placed in water and the resulting particles are collected.

Osmotic systems are also available where osmotic pressure is employed as the driving force to afford release of a drug. Such systems generally consist of a core of drug surrounded by a semipermeable membrane containing one or more orifices. The membrane allows diffusion of water into the core, but does not allow release of the drug except through the orifices. Examples of materials used as the semipermeable membrane include polyvinyl alcohol, polyurethane, cellulose acetate, ethylcellulose, and polyvinyl chloride.

The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic or prophylatic effect, related to the desired daily or divided dose, in association with one or more suitable pharmaceutical carriers, diluents or excipients therefore to afford sustained release of active agent. With a sustained release pharmaceutical formulation of the present invention, the unit dosage form may contain an amount of moxonidine salt with an equivalent weight of moxonidine between about 0.01 to 5.0 mg. For treating hypertension, a preferred pharmaceutical formulation contains an equivalent of moxonidine between about 0.5 to about 1.5 mg, administered daily.

The sustained release formulations of the present invention should provide a prophylatic or therapeutic amount of moxonidine to a patient to achieve, and then maintain, an effective dose of active agent with diminished undesirable effects. These formulations should achieve a more idealized spatial placement and temporal delivery of moxonidine, particularly temporal delivery. Spatial placement, of course, relates to targeting a pharmaceutical agent to a specific organ or tissue while temporal delivery refers to controlling the rate of drug delivery.

The following examples are provided to further illustrate the present invention. The examples are illustrative only and are not intended to limit the scope of the present invention.

Example 1
Moxonidine Salts

Various moxonidine salts were synthesized and then characterized as follows:

Example 1A - Moxonidine Hydrochloride Hydrate

Moxonidine (25 grams) and isopropyl alcohol (125 mL) were combined in a 250 mL round-bottomed flask to form a slurry. Following addition of 8.75 mL of concentrated hydrochloric acid to the slurry, the slurry was stirred for one hour at ambient temperature and then for one hour in an ice bath. The product was isolated by filtration, was rinsed with chilled isopropyl alcohol and then dried in vacuo overnight at room temperature to give 29.6 g of a white solid.

The potency was determined to be 81% (82% theoretical) by high performance liquid chromatography (HPLC). Recovery was 96%.

X-ray powder diffraction analysis showed that the X-ray powder diffraction pattern for this white solid was distinct from that of moxonidine.

This material showed by thermogravimetric analysis (TGA) a loss of 9.4% of its mass upon heating to 180°C.

Further, this material showed through differential scanning colorimetry (DSC) endothermic transitions at approximately 127°C and 155°C followed by exothermic transitions at approximately 169°C and 187°C.

Example 1B - DiMoxonidine Sulfate

Moxonidine (40.0 grams) and ethanol (350 mL, containing 5% water and 5% methanol) were combined and heated to 45 °C. A solution of 8.4 grams of concentrated sulfuric acid in 50 mL of ethanol was then added. The mixture was allowed to cool slowly to ambient temperature and the product was isolated by filtration. It was washed with ethanol and dried overnight in

vacuo at 40 °C to give 37.2 grams of a white solid. Potency was determined to be 83% (83% theoretical). The unique X-ray powder pattern indicated the material to be crystalline. TGA showed a loss of 0.7% of its mass upon heating to 150 °C. DSC showed an exothermic transition at 215 °C.

Example 1C - DiMoxonidine-L-Tartrate

Thirty grams of moxonidine and 200 mL of ethanol (containing 5% water and 5% methanol) were combined and heated to 55 °C. L-tartaric acid (9.52 grams) was added along with an additional 100 mL of ethanol. The resulting slurry was stirred for one half hour at 60 °C, was cooled to ambient temperature, and was filtered. After washing with ethyl acetate, the wetcake was added back to the flask and 300 mL of ethyl acetate was added. The mixture was heated at reflux for one hour. The product was isolated by cooling to ambient temperature and filtering and washing the mixture. After drying for a day in vacuo at 40 °C, 38.4 grams of white solid was obtained.

The potency was determined to be 76% (76% theoretical). The unique X-ray powder pattern indicated the material to be crystalline. TGA showed no loss upon heating up to 210 °C. DSC showed an exothermic transition at 214 °C.

Example 1D - DiMoxonidine Fumarate

Moxonidine (25 grams) and fumaric acid (6.26 grams) were combined with 250 mL of methanol and the mixture was heated to 50 °C. After a one hour stir, the mixture was cooled to ambient temperature, stirred for 3 hours, filtered, and the product was rinsed with methanol and dried overnight at 55 °C. A white powder weighing 30.6 grams was obtained.

The potency was determined to be 80% (81% theoretical). The unique X-ray powder pattern indicated the material to be

crystalline. TGA showed a loss in mass of 0.2% up to a temperature of 200 °C. DSC showed an exothermic transition at 236°C.

Example 1E - DiMoxonidine Succinate

Moxonidine (25.0 grams) and succinic acid (6.37 grams) were combined with 220 mL of methanol. The mixture was heated for one hour at 50 °C and cooled to ambient temperature. After stirring for 2 hours, the product was isolated by filtration, was rinsed with methanol, and was dried overnight at 55 °C to give 30.75 grams of white solid.

The potency was determined to be 78% (80% theoretical). The unique X-ray powder pattern indicated the material to be crystalline. TGA showed a loss of 0.11% of the mass up to 175 °C. DSC showed an endothermic transition at 220 °C and an exothermic transition at 222 °C.

Example 1F - DiMoxonidine Oxalate

Moxonidine (25.0 grams) and oxalic acid (4.76 grams) were combined with 200 mL of methanol. After stirring for 3 hours at ambient temperature, the product was isolated by filtration, was rinsed with methanol, and was dried overnight in vacuo at 55 °C followed by drying at 60 °C for 4 hours. The resulting white solid had a weight of 26.4 grams.

The potency was determined to be 84% (84% theoretical). The unique X-ray powder pattern indicated the material to be crystalline. TGA showed no loss of mass up to 200°C.

Example 1G - Moxonidine Oxalate

Moxonidine (25.0 grams) and oxalic acid (9.55 grams) were combined with 200 mL of isopropyl alcohol. After stirring for 3 hours at ambient temperature, the product was isolated by filtration, was rinsed with isopropyl alcohol, and was dried

overnight in vacuo at 55 °C followed by drying at 60 °C for 4 hours. The white solid had a weight of 33.6 grams.

The potency was determined to be 72% (73% theoretical). The unique X-ray powder pattern indicated the material to be crystalline. TGA showed no loss of mass up to 195°C.

Example 1H - DiMoxonidine Adipate

Moxonidine (25.0 grams) and adipic acid (7.88 grams) were combined with 200 mL of isopropyl alcohol. The mixture was heated for one hour at 50 °C, cooled to ambient temperature, and stirred for 3 hours. The product was isolated by filtration, was rinsed with isopropyl alcohol, and was dried overnight in vacuo at 55 °C. The white solid had a weight of 31.1 grams.

The potency was determined to be 79% (77% theoretical). The unique X-ray powder pattern indicated the material to be crystalline. TGA showed no weight loss upon heating to 180 °C, then a loss of 3.1% upon heating to 205 °C. DSC showed an endothermic transition at 192 °C and an exothermic transition at 196 °C.

Example 1I - Moxonidine Benzoate

Moxonidine (25.0 grams) and benzoic acid (12.78 g) were combined with 200 mL of isopropyl alcohol. After stirring for 3 hours at ambient temperature, the product was isolated by filtration, was rinsed with isopropyl alcohol, and was dried overnight in vacuo at 70 °C followed by drying at 50 °C for 4 days. The white solid had a weight of 36.4 g.

The potency was determined to be 65% (66% theoretical). The unique X-ray powder pattern indicated the material to be crystalline. TGA showed no loss of mass when heated up to

150 °C but loss of 17 % of mass upon heating to 220 °C. DSC showed an endothermic transition at 196 °C and an exothermic transition at 200 °C.

Example 1J - Moxonidine Pamoate

Moxonidine (20 grams) and pamoic acid (32.2 grams) were combined with 100 mL of DMSO in a 250 mL round-bottomed flask. After stirring for 0.5 hours, a homogeneous yellow solution was obtained. This solution was added drop wise over 0.5 hours to 600 mL of water which was maintained at 50°C. The slurry was cooled to ambient temperature, stirred for 2 hours and filtered. The product was rinsed with about 100 mL of water and the wetcake was combined with 500 mL of fresh water and the resulting mixture was stirred at ambient temperature overnight. The product was isolated by filtration, washing with 100 mL of water, and drying for 3 days at 50°C in vacuo. The yield of yellow solid was 51.2 grams.

The potency by HPLC was 38% (theory is 37%) and the recovery was 97%. This material showed a unique X-ray powder diffraction pattern, a loss upon heating to 140°C of 2.9% by TGA, and endothermic transitions at approximately 165 and 191°C followed by an exothermic transition at approximately 203°C by DSC. The monohydrate contains 2.8% water by theory. Proton NMR analysis indicated a 1:1 ratio of moxonidine and pamoate resonances.

Example 1K - DiMoxonidine Pamoate

Moxonidine (30g) and 200 mL of methanol were combined in a 500 mL round-bottomed flask and the slurry was heated to 55°C. Pamoic acid (24.4 g) was added in portions and was rinsed in with an additional 150 mL of methanol. The mixture was heated to 60°C to obtain a homogeneous yellow solution which, upon extended stirring produced a slurry. After a stir of 0.5 hours, the mixture was cooled over 1 hour to ambient

temperature and stirred for 2 hours. The mixture was filtered and the product was rinsed with methanol. Drying for 3 days at 30°C in vacuo produced 50.5 g of a yellow solid.

The potency by HPLC was 53% (theory is 55%) and the recovery was 93%. This material showed a unique X-ray powder diffraction pattern and no loss upon heating to 230°C by TGA. Analysis by DSC showed no endothermic transitions, just an exothermic one at approximately 235°C. Proton NMR analysis indicated a 2:1 ratio of moxonidine to pamoate resonances.

Example 1L - Moxonidine Stearate

Moxonidine (19.66 g) and stearic acid (23.67 g) were combined with 100 mL of methanol in a 500 mL round-bottomed flask and the mixture was heated to 50°C. The mixture was cooled to 40°C and 100 mL of water was added over 1 hour. The slurry was stirred for 2 hours at ambient temperature, filtered, and the product was washed with 90 mL of 1:1 methanol/water. The white solid was dried overnight in vacuo at 34°C followed by a day at 40°C to give 41.74 grams. The potency by HPLC was 44% (theory is 46%) and the recovery was 97%.

This material showed a unique X-ray powder diffraction pattern, no loss upon heating to 175°C by TGA, and an endothermic transition at approximately 80°C followed by exothermic transition at approximately 199°C by DSC. Proton NMR analysis indicated a 1:1 ratio of moxonidine and stearate resonances.

Analytical Techniques

The moxonidine salts of Example 1A-1L were analyzed using the following techniques.

High performance liquid chromatography (HPLC) was performed on a Zorbax RX-C8 column (25 cm by 4.6 mm, 5 micron), eluted at 1.0 mL/min of eluent comprised of 17%

acetonitrile and 83% aqueous solution (3.2 g sodium pentanesulfonic acid in 1L of water, conc. H_2SO_4 to pH 3). Detection was by UV at 230 nm. Moxonidine elutes at approximately 8 min. HPLC was performed on a Zorbax RX-C8 column (25 cm by 4.6 mm, 5 micron), eluted at 1.0 mL/min of eluent comprised of 17% acetonitrile and 83% aqueous solution (3.2 g sodium pentanesulfonic acid in 1L of water, conc. H_2SO_4 to pH 3). Detection was by UV at 230 nm. Moxonidine elutes at approximately 8 minutes.

For potency measurements, standard solutions of moxonidine in eluent (between 0.05 and 1.0 mg/mL) were prepared and area counts from solutions of the salts were compared to the area of the standard solutions.

For aqueous solubility measurements, enough of the salts were stirred with water at 23 °C to maintain a slight excess of solid. After 1-2 hours, the mixtures were filtered and the filtrate diluted appropriately with eluent and injected on the HPLC.

For nuclear magnetic resonance (NMR) analysis, solutions of approximately 20 mg of the salts in approximately 0.7 mL of DMSO-d_6 were analyzed on a Bruker AC-300 spectrometer, operating at a proton frequency of 300 MHz. with a delay of 5 seconds between pulses.

X-ray powder diffraction patterns (XRPD) were obtained on a Siemens D5000 X-ray powder diffractometer, equipped with a Cu Kα source (λ= 1.54056 Å) operating at 50kV and 40mA. A Kevex solid state detector was used. The diffraction patterns of the samples were obtained from 4 to 35° 2θ with a step size of 0.04° and a scanning time of 2.5 sec/step.

Thermogravimetric analyses (TGA) were conducted using a TA Instruments Model 2950. Samples were heated in open

aluminum pans from 25 to 300°C at a heating rate of 10°C/min.

Differential scanning calorimetry (DSC) was conducted on a TA Instruments Model 2920. Samples were heated in crimped aluminum pans from 30 to 300 °C at a heating rate of 5 °C/min.

Example 2

Solubility Testing

The solubilities of the moxonidine salts of the present invention, as described in Examples 1A - 1L, were measured and compared to the measured solublities for moxonidine (free base) and for previously known moxonidine salts.

Solubility was determined using conventional methods. The results of the solubility tests are provided below.

COMPOUND	WATER SOLUBILITY (mg/mL at 23 °C)
DiMoxonidine-L-Tartrate	120
*Moxonidine Hydrochloride Hydrate	101
*DiMoxonidine Sulfate	68
*DiMoxonidine Oxalate	44
*DiMoxonidine Adipate	44
*Moxonidine Oxalate	41
*Moxonidine Benzoate	8.3
*DiMoxonidine Succinate	3.3
*Moxonidine Free Base	1.3
*DiMoxonidine Fumarate	1.0
Moxonidine Stearate	0.47
Moxonidine Palmitate	0.42
DiMoxonidine Pamoate	0.10
Moxonidine Pamoate	0.04

*indicates previously known or suggested moxonidine compounds.

These solubility test results clearly demonstrate that the moxonidine salts of the present invention are low solubility in water and have solubilities significantly lower than those measured for moxonidine in its free base form and for previously known or suggested moxonidine salts.

Example 3

Preparation of Moxonidine Pharmaceutical Compositions

The moxonidine salts of examples 1A-1L and moxonidine free base were then formed into tablets. In this procedure, the moxonidine salt or moxonidine free base and a portion of the lactose monohydrate were mixed together using a mortar and pestle. This mixture was then loaded into a high shear mixer and mixed with the glyceryl behenate, hydroxypropyl methylcellulose (K 100M Premium®), polyvinylpyrrolidone (Plasdone K 29-32®), and the remaining lactose monohydrate. Purified water was added to produce the raw granulate which was subsequently dried in a tray oven. The dried granulate was then milled using a cone mill and placed into a twin shell mixer to facilitate blending with colloidal silicon dioxide (Aerosil 200®) and magnesium stearate. The final blend was compressed into tablets using a stress/strain analyzer.

Each tablet contained the following ingredients

Ingredient	Amount (mg/tablet)
Moxonidine free base or equivalent amount of moxonidine salt	0.75
Lactose Monohydrate	89.25
Glyceryl Behenate	60
Polyvinylpyrrolidone	15
Hydroxypropyl methylcellulose	120
Colloidal Silicon Dioxide	3
Magnesium Stearate	1.8

The quantity of lactose monohydrate was adjusted on the basis of moxonidine salt potency. The sum of the moxonidine salt plus the lactose monohydrate quantities always equaled 90 mg/tablet.

Example 4

Dissolution Testing of Moxonidine Pharmaceutical Compositions

Dissolution testing was conducted, using a VanKel 7000 dissolution apparatus (basket, 10 mesh) having a VanKel 8000 sampling station, on individual tablets, formulated as described in Example 3, containing one of each of the moxonidine salts disclosed in Examples 1A - 1L. This testing was done to determine the dissolution release rate of moxonidine from each type of tablet in purified water.

Each moxonidine salt tablet tested contained an amount of moxonidine in the salt form equivalent to approximately 0.75 mg of moxonidine free base.

Dissolution testing was also performed on tablets containing 0.75 mg moxonidine free base as a control.

In this test, a tablet was placed within the dissolution apparatus basket and immersed in 900 mL of purified water at 37 ± 5 °C. The basket was then rotated at 100 rpm for the length of the test. Solution sample aliquots of 1 mL were withdrawn, using the sampling station, every two hours over a period of 20 hours.

The amount of moxonidine in each sample aliquot was then measured using an isocratic reverse-phase HPLC system (Spherisorb OD/CN, 100 x 4.6 mm I.D., 5mm) with UV detection at 256 nm. The mobile phase consisted of a buffer-methanol mixture in a ratio of 70:30 (V/V) wherein the buffer was an aqueous solution of 6.8 g of anhydrous KH_2PO_4 per liter of purified water with the pH adjusted to 2.5 by adding phosphoric acid.

The HPLC analysis used a 100 μL aliquot of a standardized aqueous moxonidine solution, having a concentration of 0.75 mg/L as a control for the HPLC analysis.

The test was performed six times for each moxonidine salt and moxonidine control composition.

During the dissolution testing, over the 20-hour test interval, each tablet tested dissolved more than 90%.

The results of this dissolution testing are provided in FIG. 1 through FIG. 3. In each of these figures, the normalized total amount of moxonidine dissolved, from the tablets of Example 3, over twenty hours for the sustained release moxonidine salts of the present invention are compared to the amounts of moxonidine (free base) and of previously suggested moxonidine salts, dissolved from the tablets of Example 3, over the test period. The data for each compound presented in these figures is normalized over the amount moxonidine released for that compound over the entire 20-hour test period.

The results of these dissolution tests also show that the moxonidine salt pharmaceutical formulations of the present invention provide for a more sustained release of moxonidine than do pharmaceutical formulations containing moxonidine free base or the previously disclosed or suggested moxonidine salts, and thus have a more controlled release, with a lower initial burst and a more constant release rate, and a more prolonged release of moxonidine with a typically longer effective release period.

CLAIMS

What is claimed is:

1. A compound, comprising a salt of moxonidine, or solvate thereof, wherein said salt has a low solubility.

2. A compound of Claim 1 wherein said salt has a solubility of less than 1.0 mg/mL.

3. A compound of Claim 1 wherein said salt has a solubility of 0.5 mg/mL or less.

4. A compound of Claim 3, which is moxonidine stearate or a solvate thereof.

5. A compound of Claim 3, which is moxonidine palmitate or a solvate thereof.

6. A compound of Claim 3 wherein said salt has a water solubility of less than about 0.15 mg/mL.

7. A compound of Claim 6, which is moxonidine pamoate or a solvate thereof.

8. A compound of Claim 7, which is dimoxonidine pamoate or a solvate thereof.

9. A pharmaceutical formulation, for the sustained release of moxonidine, comprising an effective dose of a low solubility moxonidine salt, or a solvate thereof, in association with one or more carriers, diluents or excipients.

10. The formulation of Claim 9 wherein said formulation is an oral dosage form.

11. The formulation of Claim 9, further comprising a unit dose of moxonidine salt in an amount equivalent to about 0.01 mg to about 5.0 mg of moxonidine.

12. A formulation of Claim 8 wherein said formulation is a formulation for the sustained release of the moxonidine salt.

13. A method of treating hypertension, comprising administering to a mammal in need thereof an effective dose of a low solubility moxonidine salt or a solvate thereof.

14. A method of Claim 13 wherein said salt is administered in the form of a pharmaceutical formulation in association with one or more carriers, diluents or excipients.

15. A method of Claim 13 wherein said salt has a water solubility of less than about 0.5 mg/mL.

16. A method of Claim 15 wherein said salt comprises moxonidine stearate.

17. A method of Claim 15 wherein said salt is moxonidine palmitate or a solvate thereof.

18. A method of Claim 15 wherein said salt has a water solubility of less than about 0.15 mg/mL.

19. A method of Claim 18 wherein said salt is moxonidine pamoate or a solvate thereof.

20. A method of Claim 18 wherein said salt is dimoxonidine pamoate or a solvate thereof.

21. A method of treating left ventricular hypertrophy, comprising administering to a mammal in need thereof an effective dose of a low solubility moxonidine salt or a solvate thereof.

22. The use of a low solubility salt of moxonidine, as a solvate thereof, in the preparation of a sustained release medicament.

23. A use of Claim 22 wherein said salt has a water solubility of less than about 0.5 mg/mL.

24. A use of Claim 23 wherein said salt is moxonidine stearate or a solvate thereof.

25. A use of Claim 23 wherein said salt is moxonidine palmitate or a solvate thereof.

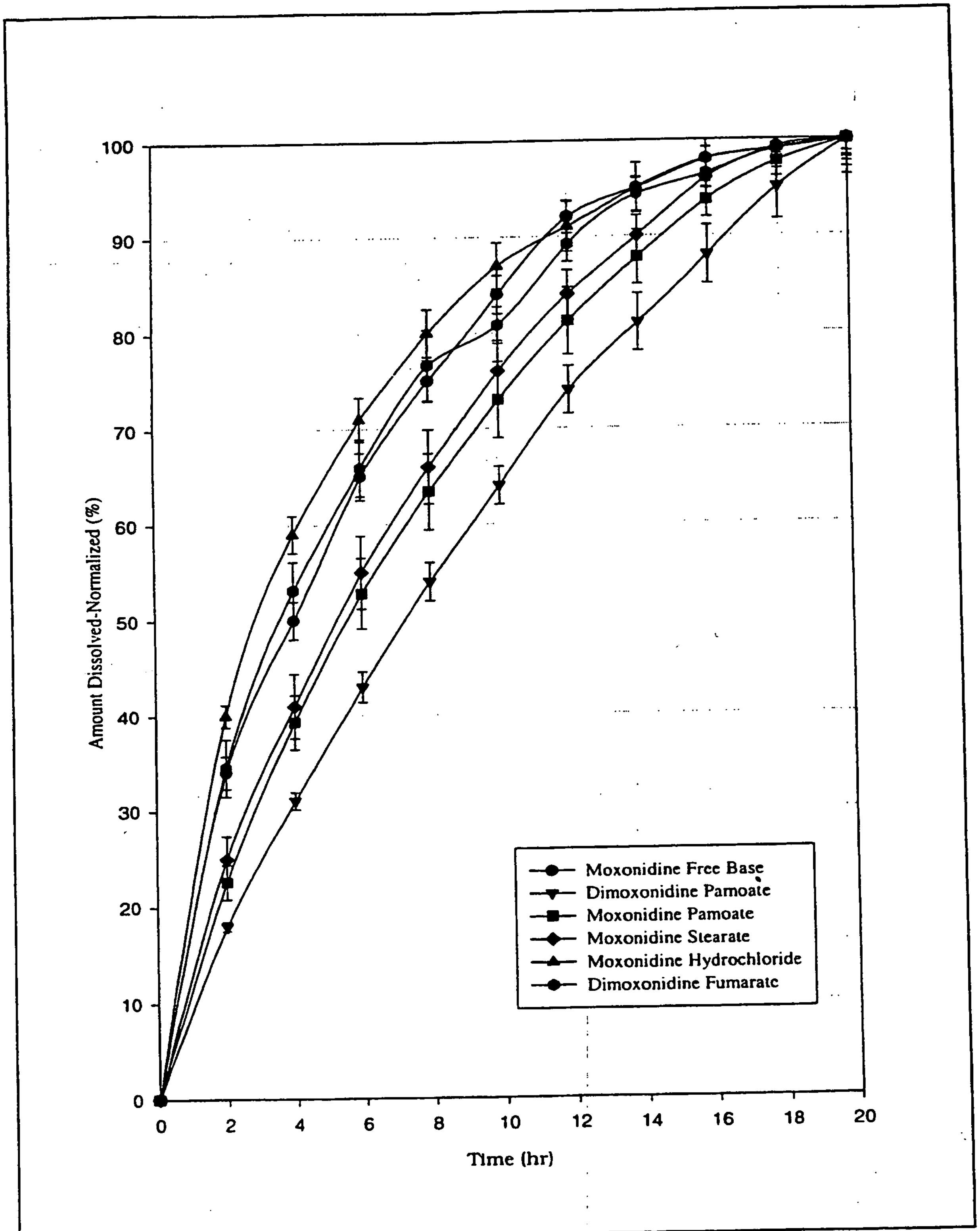
26. A use of Claim 23 wherein said salt has a water solubility of less than about 0.15 mg/mL.

27. A use of Claim 26 wherein said salt is moxonidine pamoate or a solvate thereof.

28. A use of Claim 26 wherein said salt is dimoxonidine pamoate or a solvate thereof.

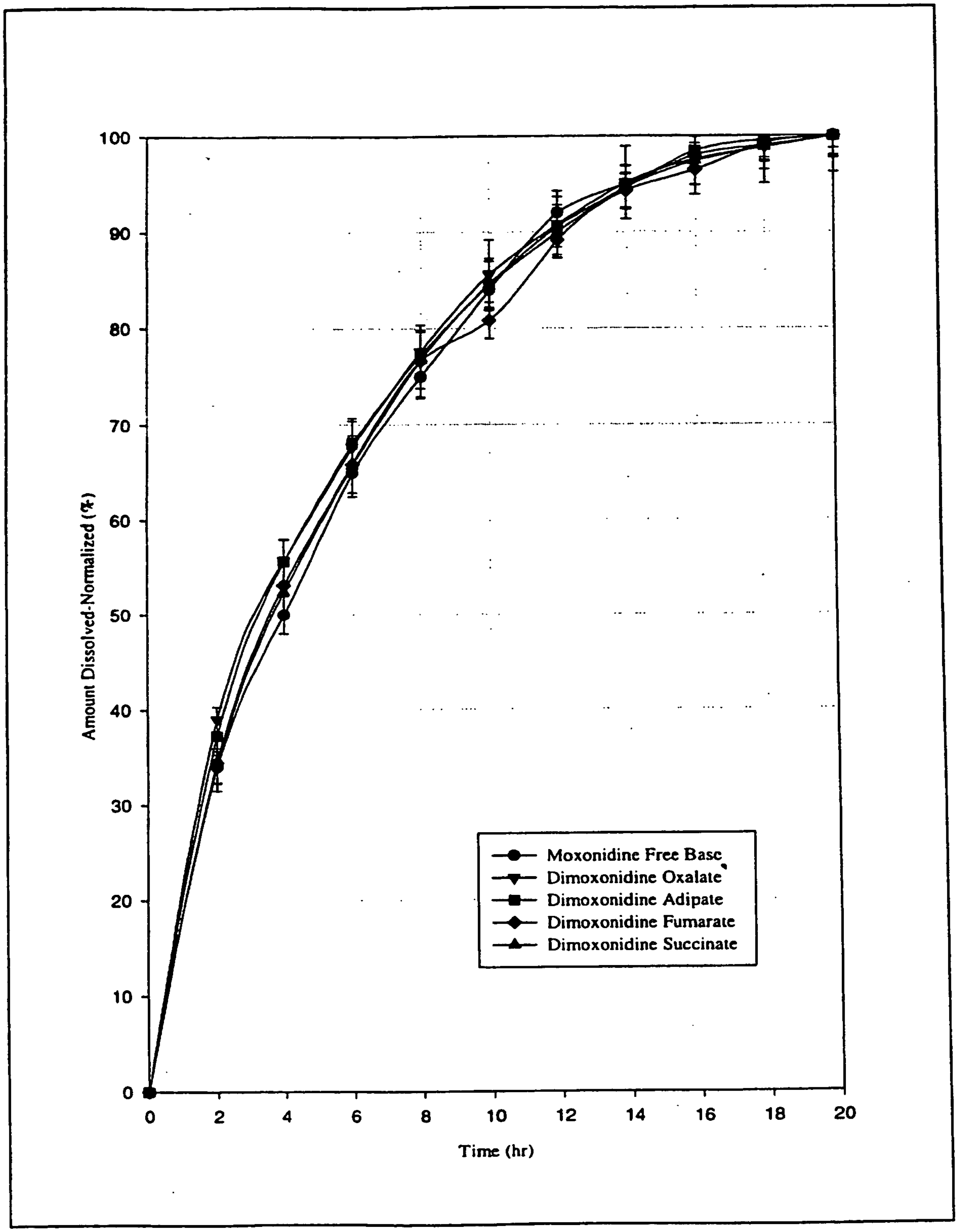
29. The use of Claim 22 wherein said medicament is useful for treating hypertension.

30. The use of Claim 22 wherein said medicament is useful for treating left ventricular hypertrophy.



Amount Dissolved-Normalized (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
Time (hr)
Moxonidine Free Base
Dimoxonidine Pamoate
Moxonidine Pamoate
Moxonidine Stearate
Moxonidine Hydrochloride
Dimoxonidine Fumarate

FIG. 1



100
90
80
70
60
50
40
30
20
10
0
Amount Dissolved-Normalized (%)
0
2
4
6
8
10
12
14
16
18
20
Time (hr)
Moxonidine Free Base
Dimoxonidine Oxalate
Dimoxonidine Adipate
Dimoxonidine Fumarate
Dimoxonidine Succinate

FIG. 2

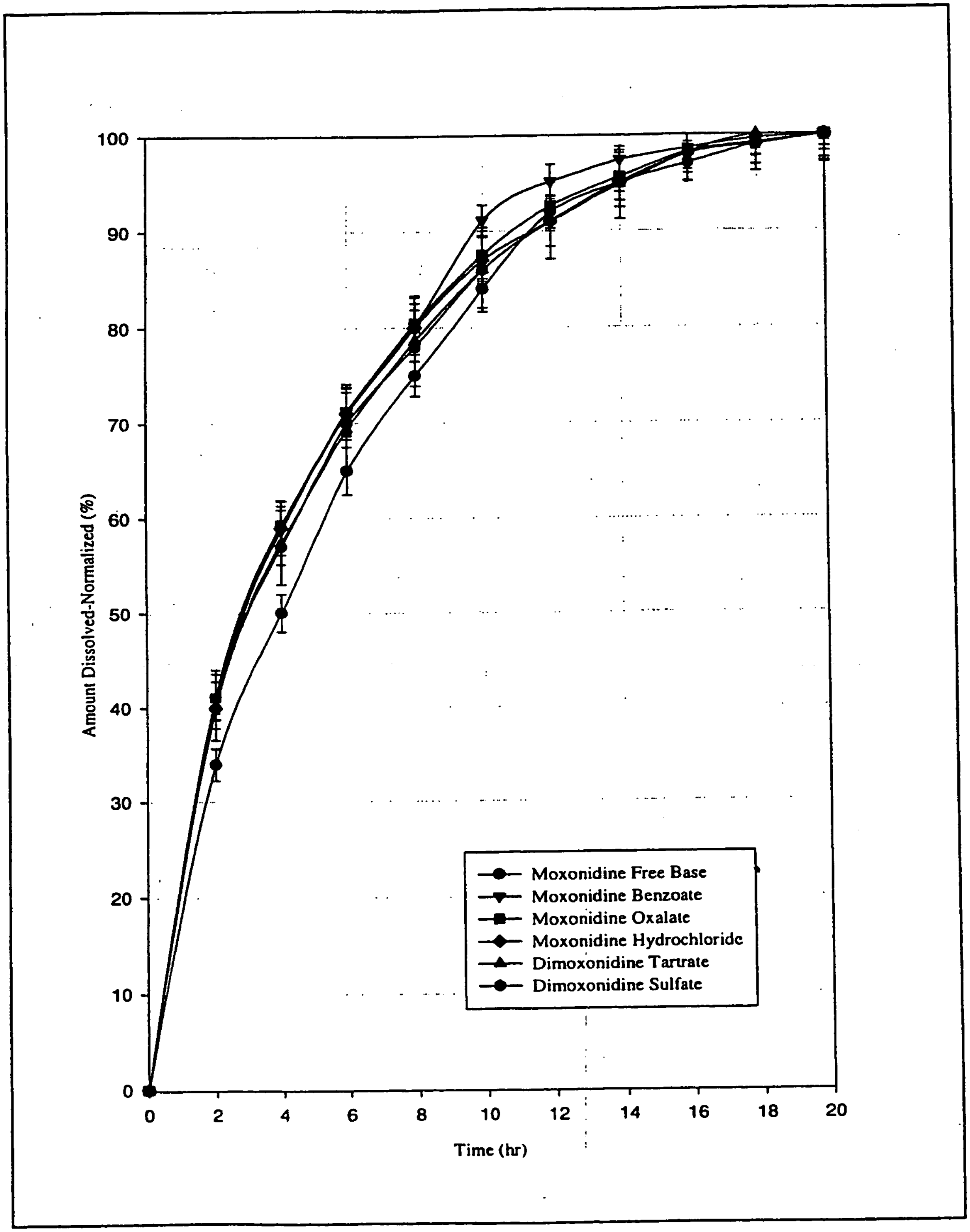

100
90
80
70
60
50
40
30
20
10
0
Amount Dissolved-Normalized (%)
0
2
4
6
8
10
12
14
16
18
20
Time (hr)
Moxonidine Free Base
Moxonidine Benzoate
Moxonidine Oxalate
Moxonidine Hydrochloride
Dimoxonidine Tartrate
Dimoxonidine Sulfate

FIG. 3

INTERNATIONAL SEARCH REPORT

Inte   .onal Application No
PCT/US 00/00968

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K47/12 A61K31/506 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 26728 A (BEIERSDORF-LILLY) 6 September 1996 (1996-09-06) claims page 2, line 10 - line 22	1,9,10, 13,14, 21,22, 29,30
A	EP 0 880 967 A (SOLVAY) 2 December 1998 (1998-12-02) claims examples page 2, line 24 - line 27	1,9,10, 13,14, 21,22, 29,30

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2000	31/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte   .onal Application No
PCT/US 00/00968

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 857 483 A (ELI LILLY) 12 August 1998 (1998-08-12) claims page 10, line 10 - line 34	1,9,10, 13,14, 21,22, 29,30
A	EP 0 689 837 A (KALI-CHEMIE) 3 January 1996 (1996-01-03) cited in the application claims examples page 2, line 23 - line 26	1,9,10, 13,14, 21,22, 29,30
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A	WO 97 46241 A (ELI LILLY) 11 December 1997 (1997-12-11) cited in the application claims examples page 17, line 20 -page 18, line 13	1,9,10, 13,14, 21,22, 29,30

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/00968

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/00968

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